

We Claim:

- 1 1. A solid pharmaceutical dosage form for oral administration, the dosage form
2 comprising:
3 an extended release layer comprising a biguanide; and
4 an immediate release layer comprising a glitazone.
- 1 2. The dosage form of claim 1, wherein the biguanide comprises one or more of
2 metformin, phenformin, and buformin.
- 1 3. The dosage form of claim 1, wherein the biguanide is metformin.
- 1 4. The dosage form of claim 1, wherein the glitazone comprises one or more of
2 pioglitazone, rosiglitazone, troglitazone, ciglitazone and englitazone.
- 1 5. The dosage form of claim 4, wherein the glitazone is pioglitazone.
- 1 6. The dosage form of claim 1, wherein after oral administration the biguanide is
2 released over a period of about 4 to about 36 hours.
- 1 7. The dosage form of claim 6, wherein the biguanide is released over a period of
2 about 8 to about 24 hours.
- 1 8. The dosage form of claim 1, wherein the dosage form comprises tablets or
2 capsules.
- 1 9. The dosage form of claim 8, wherein the tablet includes a coating.
- 1 10. The dosage form of claim 8, wherein the capsules include one or more of pellets,
2 beads, granules, multiparticulates, tablets and powder.
- 1 11. The dosage form of claim 1, wherein the extended release layer comprises a
2 matrix.
- 1 12. The dosage form of claim 11, wherein the matrix comprises a uniform mixture of
2 the biguanide and one or more rate controlling polymers.

- 1 13. The dosage form of claim 12, wherein the one or more rate-controlling polymers
2 comprises hydrophilic polymers, hydrophobic polymers, or a combination
3 thereof.
- 1 14. The dosage form of claim 11, wherein the matrix further comprises one or more
2 pharmaceutically acceptable excipients.
- 1 15. The dosage form of claim 14, wherein the pharmaceutically acceptable excipients
2 comprise one or more of diluents, lubricants, disintegrants, binders, glidants,
3 coloring and flavoring agents.
- 1 16. The dosage form of claim 1, wherein the biguanide is layered onto a
2 pharmaceutically inert core or seed.
- 1 17. The dosage form of claim 16, wherein the inert core or seed is hydrosoluble or
2 hydroinsoluble.
- 1 18. The dosage form of claim 1, wherein the immediate release outer layer further
2 comprises film-forming polymers and optionally other pharmaceutically
3 acceptable excipients.
- 1 19. The dosage form of claim 18, wherein the film-forming polymers are water-
2 soluble polymers.
- 1 20. The dosage form of claim 18, wherein the pharmaceutically acceptable excipients
2 comprises one or more of plasticizers, opacifiers and colorants.
- 1 21. The dosage form of claim 1, further comprising one or more of sulfonylurea,
2 insulin, alpha-glucosidase inhibitors, meglitinides, fibrates, statins, squalene
3 synthesis inhibitors and angiotensin-converting enzyme inhibitors.
- 1 22. The dosage form of claim 1, further comprising a wetting agent in the immediate
2 release layer, wherein the immediate release layer comprises the glitazone and the
3 wetting agent in a weight ratio ranging from about 10:1 to about 1:25.

- 1 23. The dosage form of claim 22, wherein the wetting agent is selected from amongst
2 hydrophilic and hydrophobic surfactants.
- 1 24. The dosage form of claim 23, wherein the hydrophilic surfactants are selected
2 from one or more of non-ionic surfactants, ionic surfactants or mixtures thereof.
- 1 25. The dosage form of claim 23, wherein the hydrophobic surfactants are selected
2 from one or more of alcohols; polyoxyethylene alkylethers; fatty acids; glycerol
3 fatty acid monoesters; glycerol fatty acid diesters; acetylated glycerol fatty acid
4 monoesters; acetylated glycerol fatty acid diesters, lower alcohol fatty acid esters;
5 polyethylene glycol fatty acid esters; polyethylene glycol glycerol fatty acid
6 esters; polypropylene glycol fatty acid esters; polyoxyethylene glycerides; lactic
7 acid derivatives of monoglycerides; lactic acid derivatives of diglycerides;
8 propylene glycol diglycerides; sorbitan fatty acid esters; polyoxyethylene sorbitan
9 fatty acid esters; polyoxyethylene-polyoxypropylene block copolymers,
10 polyethyleneglycols as esters or ethers, polyethoxylated castor oil;
11 polyethoxylated hydrogenated castor oil, polyethoxylated fatty acid from castor
12 oil or polyethoxylated fatty acid from castor oil or polyethoxylated fatty acid from
13 hydrogenated castor oil.
- 1 26. The dosage form of claim 24, wherein the non-ionic surfactants are selected from
2 one or more of alkylglucosides; alkylmaltosides; alkylthioglucosides; lauryl
3 macrogolglycerides; caprylocaproyl macrogolglycerides, polyoxyethylene alkyl
4 ethers; polyoxyethylene alkylphenols; polyethylene glycol fatty acid esters;
5 polyethylene glycol glycerol fatty acid esters; polyoxyethylene sorbitan fatty acid
6 esters; polyoxyethylene-polyoxypropylene block copolymers; polyglycerol fatty
7 acid esters; polyoxyethylene glycerides; polyoxyethylene sterols, derivatives, and
8 analogues thereof; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated
9 vegetable oils; reaction products of polyols and at least one member of the group
10 consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils,
11 and sterols; sugar esters, sugar ethers; sucroglycerides; and mixtures thereof.

- 1 27. The dosage form of claim 24, wherein the ionic surfactants are selected from one
2 or more of alkyl ammonium salts; bile acids and salts, analogues, and derivatives
3 thereof; fatty acid derivatives of amino acids, oligopeptides, and polypeptides;
4 glyceride derivatives of amino acids, oligopeptides, and polypeptides; acyl
5 lactylates; monoacetylated tartaric acid esters of monoglycerides, monoacetylated
6 tartaric acid esters of diglycerides, diacetylated tartaric acid esters of
7 monoglycerides, diacetylated tartaric acid esters of diglycerides; succinylated
8 monoglycerides; citric acid esters of monoglycerides; citric acid esters of
9 diglycerides; alginate salts; propylene glycol alginate; lecithins and hydrogenated
10 lecithins; lysolecithin and hydrogenated lysolecithins; lysophospholipids and
11 derivatives thereof; phospholipids and derivatives thereof; salts of alkylsulfates;
12 salts of fatty acids; sodium docusate; and mixtures thereof.
- 1 28. The dosage form of claim 1, wherein the extended release layer comprises a core
2 and the immediate release layer covers at least a portion of the core.
- 1 29. The dosage form of claim 1, wherein the dosage form comprises a bilayered
2 dosage form.
- 1 30. A process for preparing a solid, orally administered pharmaceutical dosage form
2 of an extended release core of a biguanide and an immediate release layer of a
3 glitazone, the process comprising:
4 a. dispersing the biguanide in a solid matrix to form a core having a surface; and
5 b. layering the immediate release layer of the glitazone on the surface of the
6 core.
- 1 31. The process of claim 30, wherein layering the immediate release layer further
2 comprises layering one or more wetting agents.
- 1 32. The process of claim 31, wherein the glitazone and the one or more wetting
2 agents are present in the immediate release layer in a weight ratio ranging from
3 about 10:1 to about 1:25.

- 1 33. The process of claim 31, wherein the one or more wetting agents are selected
2 from amongst hydrophilic or hydrophobic surfactants.
- 1 34. The process of claim 33, wherein the hydrophilic surfactants are selected from
2 one or more of non-ionic surfactants, ionic surfactants or mixtures thereof.
- 1 35. The process of claim 33, wherein the hydrophobic surfactants are selected from
2 one or more of alcohols; polyoxyethylene alkylethers; fatty acids; glycerol fatty
3 acid monoesters; glycerol fatty acid diesters; acetylated glycerol fatty acid
4 monoesters; acetylated glycerol fatty acid diesters, lower alcohol fatty acid esters;
5 polyethylene glycol fatty acid esters; polyethylene glycol glycerol fatty acid
6 esters; polypropylene glycol fatty acid esters; polyoxyethylene glycerides; lactic
7 acid derivatives of monoglycerides; lactic acid derivatives of diglycerides;
8 propylene glycol diglycerides; sorbitan fatty acid esters; polyoxyethylene sorbitan
9 fatty acid esters; polyoxyethylene-polyoxypropylene block copolymers,
10 polyethyleneglycols as esters or ethers, polyethoxylated castor oil;
11 polyethoxylated hydrogenated castor oil, polyethoxylated fatty acid from castor
12 oil or polyethoxylated fatty acid from castor oil or polyethoxylated fatty acid from
13 hydrogenated castor oil.
- 1 36. The process of claim 34, wherein the non-ionic surfactants are selected from one
2 or more of alkylglucosides; alkylmaltosides; alkylthioglucosides; lauryl
3 macrogolglycerides; caprylocaproyl macrogolglycerides, polyoxyethylene alkyl
4 ethers; polyoxyethylene alkylphenols; polyethylene glycol fatty acid esters;
5 polyethylene glycol glycerol fatty acid esters; polyoxyethylene sorbitan fatty acid
6 esters; polyoxyethylene-polyoxypropylene block copolymers; polyglycerol fatty
7 acid esters; polyoxyethylene glycerides; polyoxyethylene sterols, derivatives, and
8 analogues thereof; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated
9 vegetable oils; reaction products of polyols and at least one member of the group
10 consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils,
11 and sterols; sugar esters, sugar ethers; sucroglycerides; and mixtures thereof.

- 1 37. The process of claim 34, wherein the ionic surfactants are selected from one or
2 more of alkyl ammonium salts; bile acids and salts, analogues, and derivatives
3 thereof; fatty acid derivatives of amino acids, oligopeptides, and polypeptides;
4 glyceride derivatives of amino acids, oligopeptides, and polypeptides; acyl
5 lactylates; monoacetylated tartaric acid esters of monoglycerides, monoacetylated
6 tartaric acid esters of diglycerides, diacetylated tartaric acid esters of
7 monoglycerides, diacetylated tartaric acid esters of diglycerides; succinylated
8 monoglycerides; citric acid esters of monoglycerides; citric acid esters of
9 diglycerides; alginate salts; propylene glycol alginate; lecithins and hydrogenated
10 lecithins; lysolecithin and hydrogenated lysolecithins; lysophospholipids and
11 derivatives thereof; phospholipids and derivatives thereof; salts of alkylsulfates;
12 salts of fatty acids; sodium docusate; and mixtures thereof.
- 1 38. The process of claim 30, wherein the biguanide is selected from one or more of
2 metformin, phenformin and buformin.
- 1 39. The process of claim 30, wherein the biguanide comprises metformin.
- 1 40. The process of claim 30, wherein the glitazone is selected from one or more of
2 pioglitazone, rosiglitazone, troglitazone, ciglitazone and englitazone.
- 1 41. The process of claim 30, wherein the glitazone comprises pioglitazone.
- 1 42. The process of claim 30, wherein after oral administration the biguanide is
2 released over a period of about 4 to about 36 hours.
- 1 43. The process of claim 42, wherein the biguanide is released over a period of about
2 8 to about 24 hours.
- 1 44. The process of claim 30, further comprising forming a tablet or a capsule.
- 1 45. The process of claim 44, further comprising coating the tablet.
- 1 46. The process of claim 44, wherein the capsule contains one or more of pellets,
2 beads, granules, multiparticulates, tablets and powder.

- 1 47. The process of claim 48 wherein the core comprises a matrix.
- 1 48. The process of claim 30, wherein the matrix comprises a uniform mixture of the
2 biguanide and one or more rate controlling polymers.
- 1 49. The process of claim 48, wherein the one or more rate-controlling polymers may
2 be either or both of hydrophilic and hydrophobic.
- 1 50. The process of claim 30, wherein the matrix further comprises one or more
2 pharmaceutically acceptable excipients.
- 1 51. The process of claim 50, wherein the pharmaceutically acceptable excipients
2 comprise one or more of diluents, lubricants, disintegrants, binders, glidants,
3 colorants, and flavorants.
- 1 52. The process of claim 30, wherein the biguanide is layered onto pharmaceutically
2 inert core or seeds.
- 1 53. The process of claim 52, wherein the inert core or seeds are hydrosoluble or
2 hydroinsoluble.
- 1 54. The process of claim 30, wherein the immediate release outer layer further
2 comprises film-forming polymers and optionally other pharmaceutically
3 acceptable excipients.
- 1 55. The process of claim 54, wherein the film-forming polymers comprise water-
2 soluble polymers.
- 1 56. The process of claim 54, wherein the pharmaceutically acceptable excipients
2 comprise one or more of plasticizers, opacifiers and colorants.
- 1 57. The process of claim 30, further comprising placing a seal-coat over the core,
2 wherein the seal-coat comprises hydrophilic polymers.
- 1 58. A process for preparing a bilayered, solid, orally administered pharmaceutical
2 dosage form of a biguanide and a glitazone, the process comprising:

- 3 a. dispersing the biguanide in an extended release carrier base material;
4 b. separately dispersing the glitazone in an immediate release carrier base
5 material; and
6 c. compressing the material of step a and step b to form bilayered tablet.

1 59. The process of claim 58, wherein the immediate release carrier base material
2 further comprises one or more wetting agents before or after dispersing the
3 glitazone.

1 60. The process of claim 59, wherein the glitazone and the one or more wetting
2 agents are present in a weight ratio ranging from about 10:1 to about 1:25.

1 61. The process of claim 59, wherein the one or more wetting agents are selected
2 from amongst hydrophilic or hydrophobic surfactants.

1 62. The process of claim 61, wherein the hydrophilic surfactants are selected from
2 one or more of non-ionic surfactants, ionic surfactants or mixtures thereof.

1 63. The process of claim 61, wherein the hydrophobic surfactants are selected from
2 one or more of alcohols; polyoxyethylene alkylethers; fatty acids; glycerol fatty
3 acid monoesters; glycerol fatty acid diesters; acetylated glycerol fatty acid
4 monoesters; acetylated glycerol fatty acid diesters, lower alcohol fatty acid esters;
5 polyethylene glycol fatty acid esters; polyethylene glycol glycerol fatty acid
6 esters; polypropylene glycol fatty acid esters; polyoxyethylene glycerides; lactic
7 acid derivatives of monoglycerides; lactic acid derivatives of diglycerides;
8 propylene glycol diglycerides; sorbitan fatty acid esters; polyoxyethylene sorbitan
9 fatty acid esters; polyoxyethylene-polyoxypropylene block copolymers,
10 polyethyleneglycols as esters or ethers, polyethoxylated castor oil;
11 polyethoxylated hydrogenated castor oil, polyethoxylated fatty acid from castor
12 oil or polyethoxylated fatty acid from castor oil or polyethoxylated fatty acid from
13 hydrogenated castor oil.

1 64. The process of claim 62, wherein the non-ionic surfactants are selected from the
2 one or more of alkylglucosides; alkylmaltosides; alkylthioglucosides; lauryl

3 macrogolglycerides; caprylocaproyl macrogolglycerides, polyoxyethylene alkyl
4 ethers; polyoxyethylene alkylphenols; polyethylene glycol fatty acid esters;
5 polyethylene glycol glycerol fatty acid esters; polyoxyethylene sorbitan fatty acid
6 esters; polyoxyethylene-polyoxypropylene block copolymers; polyglycerol fatty
7 acid esters; polyoxyethylene glycerides; polyoxyethylene sterols, derivatives, and
8 analogues thereof; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated
9 vegetable oils; reaction products of polyols and at least one member of the group
10 consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils,
11 and sterols; sugar esters, sugar ethers; sucroglycerides; and mixtures thereof.

1 65. The process of claim 62, wherein the ionic surfactants are selected from one or
2 more of alkyl ammonium salts; bile acids and salts, analogues, and derivatives
3 thereof; fatty acid derivatives of amino acids, oligopeptides, and polypeptides;
4 glyceride derivatives of amino acids, oligopeptides, and polypeptides; acyl
5 lactylates; monoacetylated tartaric acid esters of monoglycerides, monoacetylated
6 tartaric acid esters of diglycerides, diacetylated tartaric acid esters of
7 monoglycerides, diacetylated tartaric acid esters of diglycerides; succinylated
8 monoglycerides; citric acid esters of monoglycerides; citric acid esters of
9 diglycerides; alginate salts; propylene glycol alginate; lecithins and hydrogenated
10 lecithins; lysolecithin and hydrogenated lysolecithins; lysophospholipids and
11 derivatives thereof; phospholipids and derivatives thereof; salts of alkylsulfates;
12 salts of fatty acids; sodium docusate; and mixtures thereof.

1 66. The process of claim 58, wherein the biguanide is selected from one or more of
2 metformin, phenformin and buformin.

1 67. The process of claim 58, wherein the biguanide comprises metformin.

1 68. The process of claim 58, wherein the glitazone is selected from one or more of
2 pioglitazone, rosiglitazone, troglitazone, ciglitazone and englitazone.

1 69. The process of clam 58, wherein the glitazone comprises pioglitazone.

- 1 70. The process of claim 58, wherein after oral administration the biguanide is
2 released over a period of about 4 to about 36 hours.
- 1 71. The process of claim 70, wherein the biguanide is released over a period of about
2 8 to about 24 hours.
- 1 72. The process of claim 58, further comprising forming a tablet or a capsule.
- 1 73. The process of claim 72, further comprising coating the tablet.
- 1 74. The process of claim 72, wherein the capsule contains one or more of pellets,
2 beads, granules, multiparticulates, tablets and powder.
- 1 75. The process of claim 58, wherein the biguanide layer comprises a matrix.
- 1 76. The process of claim 75, wherein the matrix comprises a uniform mixture of the
2 biguanide and one or more rate controlling polymers.
- 1 77. The process of claim 76, wherein the one or more rate-controlling polymers may
2 be either or both of hydrophilic and hydrophobic.
- 1 78. The process of claim 75, wherein the matrix further comprises one or more
2 pharmaceutically acceptable excipients.
- 1 79. The process of claim 78, wherein the pharmaceutically acceptable excipients
2 comprise one or more of diluents, lubricants, disintegrants, binders, glidants,
3 colorants, and flavorants.
- 1 80. The process of claim 58, wherein the biguanide is layered onto pharmaceutically
2 inert core or seeds.
- 1 81. The process of claim 80, wherein the inert core or seeds are hydrosoluble or
2 hydroinsoluble.

- 1 82. The process of claim 58, wherein the immediate release carrier base material
2 further comprises film-forming polymers and optionally other pharmaceutically
3 acceptable excipients.
- 1 83. The process of claim 82, wherein the film-forming polymers comprise water-
2 soluble polymers.
- 1 84. The process of claim 82, wherein the pharmaceutically acceptable excipients
2 comprise one or more of plasticizers, opacifiers and colorants.
- 1 85. The process of claim 58, further comprising providing a seal-coat of one or more
2 hydrophilic polymers between the two layers.
- 1 86. A method of treating non-insulin dependent diabetes mellitus in a patient in need
2 thereof, the method comprising administering a solid, pharmaceutical dosage
3 form of the combination of a biguanide and a glitazone, wherein the dosage form
4 provides an extended-release of the biguanide and an immediate release of the
5 glitazone.
- 1 87. The method of claim 86, wherein the biguanide comprises one or more of
2 metformin, phenformin, and buformin.
- 1 88. The method of claim 86, wherein the biguanide is metformin.
- 1 89. The method of claim 86, wherein the glitazone comprises one or more of
2 pioglitazone, rosiglitazone, troglitazone, ciglitazone and englitazone.
- 1 90. The method of claim 86 wherein the glitazone is pioglitazone.
- 1 91. The method of claim 86, wherein after oral administration the biguanide is
2 released over a period of about 4 to about 36 hours.
- 1 92. The method of claim 86, wherein the biguanide is released over a period of about
2 8 to about 24 hours.
- 1 93. The method of claim 86, wherein the dosage form comprises tablets or capsules.

- 1 94. The method of claim 86, wherein the dosage form further comprises one or more
2 of sulfonylurea, insulin, alpha-glucosidase inhibitors, meglitinides, fibrates,
3 statins, squalene synthesis inhibitors and angiotensin-converting enzyme
4 inhibitors.